

TESTING TIMES

Bandolier has long been concerned about diagnostic testing. We have argued that new diagnostic tests are introduced with lower levels of evidence than new treatments, and that this plays an important part in rising health care costs.

The evidence-base for diagnostic tests, and their use as motors for change through 'technology creep' have been slippery topics, hard to grip. New information will help those who do the tests and those who use them.

Systematic review methods

A Cochrane methods working group under the direction of Les Irwig and Paul Glasziou in Australia have, within the last few weeks, posted on the Internet some recommended methods for systematic reviews of screening and diagnostic tests. The Internet address is:

<http://som.flinders.edu.au/cochrane/>

This is an important document, not because it has all the answers, but it informs us as how to seek answers about diagnostic tests. It draws together a very useful bibliography on diagnostic test evaluation and overview and has excellent guidelines on how to work. It will be an invaluable tool to move knowledge forward in this difficult subject, and, though it will take some time, it will encourage groups and individuals to begin to put the bricks into this particular wall.

Test more, find more, treat more

The importance of knowledge about diagnostic tests is demonstrated by two articles and an editorial in JAMA. Their thrust is that increase use of diagnostic tests is directly related to increases in treatments, without any rational link to need. The studies [1,2] are good examples of how observational studies from administrative data can be used to pose important questions about how we run our health service.

Invasive cardiac procedures

The first study [1] was a survey of utilisation rates for cardiac stress tests, coronary angiography and revascularisation procedures in 12 coronary angiography service areas in New England. In each area data were collected from 1992 and 1993, and then the rates of diagnostic testing and procedures correlated using the correlation of determination (R^2 , where a value of 1 means that all of the change in one parameter is determined by change in the other, and where a value of 0 means that none of it is).

Strong positive relationships were found both between testing and subsequent coronary angiography ($R^2 = 0.61$) and between coronary angiography and subsequent revascularisation ($R^2 = 0.82$).

The differences in procedures between locations were not explained by differences in prevalence, or the provision of local surgical services. The authors concluded that the relationships between testing and subsequent procedures reflect underlying uncertainty about when to test for and treat ischaemic heart disease in a population where the potential reservoir of coronary disease is huge. So strategies chosen to evaluate those with symptoms can have a dramatic effect on how much disease is discovered. Test more, find more, treat more.

Impact of diagnostic testing over time

The other study [2] was a survey of the relationship between frequency of testing in a number of different clinical situations - cardiac catheterisation, spinal imaging, mammography, swallowing studies and prostatic biopsy - in 30 million elderly Americans over a 7 year period. The bulk of the variance in therapeutic intervention rates was accounted for by diagnostic testing rates (R^2 values between 0.82 and 0.93).

The authors concluded that "a substantial increase in diagnostic testing closely tracked the increase of clinically relevant downstream procedures". They suggest that managing diagnostic tests could be an important strategy for controlling the increased use of therapeutic interventions.

Self-evident?

An accompanying editorial [3] says "studies based on administrative data are often better at raising questions than answering them". Intervention rates and judgements of appropriateness of care vary. We now know that the implications of increasing testing leading to increasing volume of care are immense.

A cardinal principle of public health is "never do a test unless you know what you are going to do with the result". This applies equally well to the introduction of new tests. As soon as they are used, the dominoes start to fall.

The problem for all of us is to know exactly where the line is that we are trying to hold. More evidence about diagnostic tests would help us find it.

References:

- 1 DE Wennberg, MA Kellett, J Dickens et al. The association between local diagnostic testing intensity and invasive cardiac procedures. *Journal of the American Medical Association* 1996 275: 1161-4.

- 2 D Verrilli, G Welch. The impact of diagnostic testing on therapeutic interventions. Journal of the American Medical Association 1996 275: 1189-91.
- 3 AM Epstein. Use of diagnostic tests and therapeutic procedures in a changing health care environment. Journal of the American Medical Association 1996 275: 1197-8.

DIAGNOSTIC STRATEGIES

The Panzer reference

Bandolier 28 examined the use of likelihood ratios (LR) for use with diagnostic tests as an alternative to figures on sensitivity and specificity. One of our eminent readers sent an email with "the Panzer reference" which he thought would be useful for readers to know of because it has many examples of diagnostic strategies using LR methods.

The book [1] is published by the American College of Physicians. As the foreword says "We are moving, somewhat haltingly, from intuitive or informal clinical judgements based on the experience of individual practitioners to a more formal process in which evidence from studies of groups of similar patients augments the judgement of practitioners. The change portends an exciting new era in medicine as it harnesses, for clinical care, currently underused information about diagnostic tests derived from intensive biomedical research".

The book first examines general issues on the characteristics of diagnostic tests, about where to find information and how to use it but then moves quickly into the specific - nearly 50 short chapters examining diagnostic strategies. Each is packed with useful information and insight - a guide book rather than a rule book.

Most doctors and many scientists involved with diagnostic procedures will find this a worthwhile read. A note of caution, though, because it isn't all as clear as it could be, and there seem to be a few leaps of faith, though the general approach is excellent.

A **Bandolier** prize (signed copy of *Bandolier - the first 20 issues*) for the first person to write with an explanation of how pre-test probabilities of hypothyroidism are arrived at in chapter 39.

Reference:

RJ Panzer, ER Black, PF Griner (Eds). Diagnostic Strategies for Common Medical Problems. 1991. American College of Physicians. 550pp. ISBN 0-943126-20-7. US\$38 (in the USA).

LR for urine dipsticks for UTI

The use of dipstick testing for urinary tract infections (UTI) was mentioned in **Bandolier** 27. The paper examined how sensitivity and specificity change with different levels of clinical suspicion [1]. We can use data from that paper to see how LRs might work.

Of 366 patients with suspected UTI, 72 were positive by laboratory urine culture with >100,000 CFU/mL as a threshold.

This prevalence of 20% is similar to that of 25% found in a UK general practice study [2]. This forms the pre-test probability

However, both reports showed that using a combination of frequencies of symptoms (dysuria, nocturia, frequency) and signs (pelvic tenderness, costovertebral angle tenderness) it was possible to increase the probability of UTI to more than 50%. The UK study used an explicit scoring system.

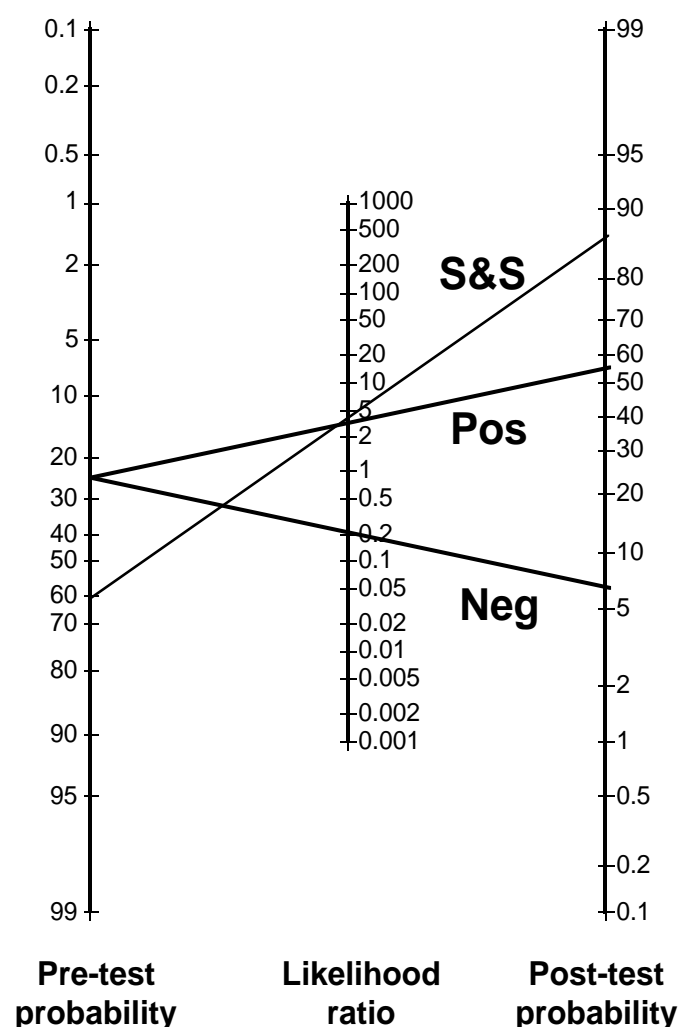
With overall sensitivity of 0.83 and specificity of 0.71, the positive LR was 3 and the negative LR was 0.2.

The nomogram shows the post-test probabilities for a patient without symptoms with a positive test (Pos - about 55%) and one with symptoms with a positive test (S&S - about 90%). The post-test probability for a patient without symptoms and a negative test (Neg) was about 5%.

One of the papers [2] indicated that a probability of above 50% represented a suitable level for initiating antibiotic treatment in cases of suspected UTI. So using symptoms plus test to generate pre-test probability and likelihood ratios respectively could be useful, and much of the data needed could be generated from audit.

Bandolier would like to hear from readers using clinical scoring symptoms for common conditions like UTI or thyroid

Likelihood ratio nomogram



disease, especially in combination with tests.

References:

- 1 MS Lachs, I Nachamkin, PH Edelstein et al. Spectrum bias in the evaluation of diagnostic tests: lessons from the rapid dipstick test for urinary tract infection. *Annals of Internal Medicine* 1992 117: 135-40.
- 2 FF Dobbs, DM Fleming. A simple scoring system for evaluating symptoms, history and urine dipstick testing in the diagnosis of urinary tract infection. *Journal of the Royal College of General Practitioners* 1987 37: 100-4.

OXFORD MASTERS PROGRAMME IN EBHC

The University of Oxford Centre for Continuing Professional Development has introduced an integrated postgraduate programme to provide education and training in the principles and practices of evidence-based health care for professionals in the NHS. The course will also be useful for those working in health care delivery or research in a commercial environment.

The programme integrates core elements of evidence-based health care into a coherent basis of expertise and competence in *using* and *establishing* evidence of health care effectiveness and efficiency.

Aim of the programme

It seeks to enable people to:

- Understand the principles of evidence-based health care.
- Identify critically appraise and incorporate results of medical and social science research into day-to-day decision making.
- Teach others how to find, appraise and implement evidence-based research.
- Design, execute, analyse and interpret clinical trials, overviews and other forms of health care evaluation.
- Undertake research in order to establish evidence where it is not available or is of uncertain quality

Structure

The Masters Programme has a layered approach with three related courses - Certificate, Diploma, MSc as shown in the box. Certificate and Diploma courses can be taken separately, but in order; Certificates lead to Diploma which lead to a Master of Science degree from the University of Oxford.

Who should do it?

Graduates (or people who have completed a professional training course), with at least five years professional work experience in health care. They should be able to bring specific work-based problems along about which they will be seeking evidence and be able to combine classroom learning with the application of the principles and practices of evidence-based health care within the workplace.

The course should be appropriate for many nurses, managers, scientists and doctors. The courses are taught in Oxford, but there are no residential requirements that we know of.

For more detailed information, contact:

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Masters Programme Content

Certificate modules:

- | | |
|----|--|
| C1 | Practice of evidence-based health care |
| C2 | Teaching evidence-based health care |
| C3 | Implementing and monitoring change in health care: |

Diploma modules:

- | | |
|----|-----------------------------------|
| D1 | Architecture of health research |
| D2 | Fundamentals of biostatistics |
| D3 | Research and protocol development |

Masters modules:

- | | |
|----|--------------------------------|
| M1 | Elective |
| M2 | Elective (both from 14 topics) |
| M3 | Thesis (25,000 words) |

DRUG TREATMENT OF PERIPHERAL ARTERIAL DISEASE

Bandolier is always interested to hear about interventions that don't work. If the evidence is strong, then we can drop the intervention and get on with thinking about things that do work. So when we were told that a drug treatment for treatment of peripheral artery disease was ineffective, we sought the evidence.

Background

Risk factors for peripheral artery disease are much the same as for cardiovascular or cerebrovascular disease. They are age, smoking, hypertension, hyperlipidaemia, diabetes, obesity, physical inactivity and family history. Of these, by far the most important is cigarette smoking; the relative risk is about 9 for those smoking more than 15 cigarettes a day.

Peripheral artery disease produces symptoms of pain, ache, cramp or severe fatigue in one or both legs occasioned by walking (intermittent claudication), so that those affected slacken their walking pace, or stop altogether. Pain-free walking distance (PFWD) on a treadmill at standard pace and incline is one of the tests used in determining disease severity.

Surgical treatments

In the 20-30% of patients who experience progressive deterioration, surgical treatments may include arterial grafts to remove the blockage in the peripheral arteries. Blockages tend to occur in large arteries with a high pressure, and at the bifurcation of arteries. In extreme cases (3-6%) amputation of the affected limb may be necessary [1].

Surgical treatments are expensive. In a paper examining the lack of information on the cost-effectiveness of drug treatments, Drummond & Davies from the Centre for Health Economics at York estimated that the average overall cost of treating limb ischaemia with a graft was between £6,600 and £11,000, depending on the site of the arterial blockage, while the cost of an amputation was close to £11,000 [2].

Naftidrofuryl

This drug has been licensed for use in peripheral vascular disease since the early 1970s at a dose of about 600 mg a day. A retrospective single-patient data analysis of five randomised controlled studies has looked at its effectiveness [3]. *Bandolier* could find no other studies or reviews in the recent (post 1990) literature apart from a single RCT which forms part of the review.

Readers should know that the work was sponsored by the manufacturer. The analysis appears to be of high standard. The authors say that they:

- made new case-record forms for all patients, with the data recorded by a person with no knowledge about whether the treatment was active or placebo
- included all demographic data, associated risk factors, and important clinical measurements

- included any critical events that occurred during the course of the study - defined as local deterioration, a cardiovascular critical event (fatal or non-fatal myocardial infarction, angina newly diagnosed, cerebrovascular accident, transient ischaemic attack or sudden death), surgical interventions (during the course of the study or immediately afterwards), and treatment discontinuation.
- included more patients than were in the original published studies to obtain an "intention-to-treat" analysis, and all patients who were randomised were included.

Studies

Five studies with 888 patients were included - 447 receiving naftidrofuryl and 441 placebo. They were double-blind parallel-group studies of three months (D1 and D2 in Germany) or 6 months duration (F1, F2 in France and GB in the UK). Patients were usually men (85%); about 60% were smokers, 23% obese, 31% had hypertension, 12% angina, 13% diabetes and 39% hyperlipidaemia. Patients in the UK had the most severe disease and the shortest PFWD. *Bandolier* could find no mention of how exercise and smoking were handled.

Outcomes and results

Efficacy was assessed on three different measures.

Pain free walking distance

Treatment was considered successful if the patients completed the full treatment period, were not lost to follow up and the PFWD increased by more than 50%. All other outcomes were considered as failures.

On an intention-to-treat basis, 175/447 treated patients achieved a successful outcome, compared with 129/441 on placebo (odds ratio 1.54, 95%CI 1.16 - 2.03). This produces a number-needed-to-treat (NNT) for one patient to benefit compared with placebo of 10.3 (95%CI 6.3 - 29).

Change in walking distance

This outcome examined the change in PFWD between the initial and final assessments, or the last visit before treatment stopped in 834 patients in whom this data was available. The analysis is shown in a L'Abbé plot for individual trials. Points above the line of equality demonstrate a positive effect of naftidrofuryl. In the paper analysis of variance showed this to be statistically significant.

Occurrence of critical cardiovascular events

These occurred in 50 patients taking placebo and 32 taking naftidrofuryl. Analysing without any exclusions, this was a significantly lower rate for naftidrofuryl (odds ratio 0.61, 95%CI 0.39 - 0.96). The NNT was 24 (13 - 266).

Comment

This was a retrospective analysis of single-patient data, regarded as being an excellent method. It did not claim to be a systematic search for all RCTs, but a recent review of naftidrofuryl [4] failed to find any other studies which ap-

proximated the stringent German guidelines for the assessment of pharmacological interventions for peripheral arterial disease.

Pain-free walking distances are a proxy measurement for some features of the illness. They may be a useful measure, because the increase ability to get about enhances the activities of daily living and quality of life. Perhaps we haven't found it yet, but there seems to be more research to be done, and good guidelines on how to do it.

Stop smoking, keep walking

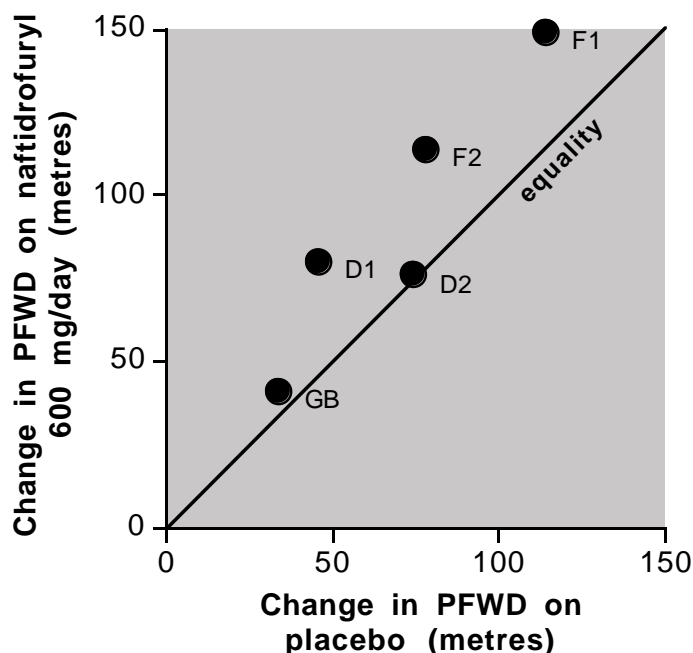
Stopping people smoking and giving them exercise training are known to be beneficial, shown in a good systematic review [5]. These are the mainstay of conservative management of intermittent claudication [1]; controlled trials of exercise increased PFWD by 88-190% in six studies, with little change in non-exercise controls [5].

Pharmacological interventions that strengthen these beneficial effects may well have its place. Systematic review of pentoxifylline also showed drug-related benefits in walking distance [5]. There is no cost-effectiveness data on which we can draw [2], but the daily drug costs are about 60p.

References:

- 1 Mecer. Drug treatment of intermittent claudication. May 1994. Vol 5 No 5.
- 2 M Drummond, L Davies. Economic evaluation of drugs in peripheral vascular disease and stroke. Journal of Cardiovascular Pharmacology 1994 23 (Suppl3) S4-S7.
- 3 P Leher, S Comte, S Gamand, TM Brown. Naftidrofuryl in intermittent claudication: a retrospective analysis. Journal of Cardiovascular Pharmacology 1994 23 (Suppl 3) S48-S52.
- 4 LB Barradell, RN Brogden. Oral naftidrofuryl. Drugs & Aging 1996 8:299-322.
- 5 K Radack, RJ Wyderski. Conservative management of intermittent claudication. Annals of Internal Medicine 1990 113: 135-46.

Effect of naftidrofuryl on change in walking distance



ABSOLUTELY THE BEST EVIDENCE EVER

Forget the endless searching for evidence of effectiveness through journals, books, or libraries, or even *Bandolier*. You can now have it all (well some of it, anyway) on your computer CD ROM. For the relatively small sum of £95 a year (plus VAT), The Cochrane Library is now available with quarterly updates.

CDSR

What is on offer is staggering. The best available evidence from regularly updated systematic reviews being done by researchers all over the world comes in the Cochrane Database of Systematic Reviews. The quality systems which are fundamental to the Collaboration ensure that these are done to the highest possible standards - and what is more, results are available at the click of a few buttons in understandable formats.

DARE

Almost as important are all the reviews done outside the Collaboration. So also in the Library is the York Database of Reviews of Effectiveness (DARE). These are structured abstracts done by professionals who have taken review papers apart and put them together again after quality filters have been applied. It also contains records of other reviews, abstracts of reports from health technology agencies around the world and abstracts of reviews from the ACP Journal Club.

CCTR

Finally there is the Cochrane Controlled Trials Register (CCTR). Contributors to the Cochrane Collaboration have identified over 100,000 controlled trials, including many not found in MEDLINE and other databases (and *Bandolier's* inside information is that before too long this could rise to 250,000).

You need

APC with 386SX processor or higher with 4MB RAM minimum and free HD space of 15MB. You don't need to be a rocket scientist or gene jockey to use it.

But all Mac users should note that a Mac version is not available because there is too little demand! This could seriously damage *Bandolier's* health - we'd like to know how many potential Mac users would want this. Don't tell us, tell the publishers.

The Cochrane Library is available from BMJ Publications (Tel 0171 383 6185/6245, Fax 0171 383 6662).

TOPICAL CAPSAICIN NNTs

Bandolier seems to get a lot of the “is X effective” or “does X really work” type of question these days. When we were asked about topical capsaicin we were relieved to find a well done systematic review which allowed the calculation of NNTs [1].

Capsaicin

This is an alkaloid from chillies that first entered European knowledge after Columbus’ second voyage to the new world in 1494. It has long been a feature of pharmacopoeias.

Recent interest concerns the use of topical capsaicin as an analgesic for conditions where pain may not be responsive to classical analgesics. There is evidence that capsaicin can deplete substance P in local sensory nerve terminals. Substance P is thought to be associated with initiation and transmission of painful stimuli, as well as a number of diseases - arthritis, psoriasis and inflammatory bowel disease.

This hypothesis gives topical capsaicin some degree of logic - remove the neurotransmitter, so remove the pain.

Does it work?

Zhang and Li Wan Po searched the literature for capsaicin papers using a sensitive strategy. They sought reports of clinical investigations. Only information from randomised, double-blind and placebo-controlled studies were used for quantitative analysis by clinical condition.

Results for the 13 trials that fulfilled these criteria and where there were extractable data are shown in the figure as a L’Abbé plot. Each symbol represents the proportion of patients in each trial reaching some clinical end-point for benefit, and the number next to the symbol the number of patients treated with topical capsaicin. Capsaicin results are plotted against placebo results. Points lying between the line of equality and the capsaicin axis are trials showing benefit. This plot is a simple representation of how similar or dissimilar trial results were found to be.

Diabetic neuropathy

Four trials reported the use of capsaicin 0.075% cream applied four times daily for 4 - 8 weeks in diabetic neuropathy. A total of 144 patients were treated with capsaicin and 165 with placebo cream. The end point was a physician global assessment of pain relief. Clinical improvement was pain completely gone, much better or better (and not no change, worse or much worse).

105/144 (73%) patients responded with capsaicin compared with 81/165 (49%) patients given placebo. The odds ratio favouring capsaicin was 2.7 (95%CI 1.7 - 4.3) and number-needed-to-treat (NNT) was 4.2 (2.9 - 7.5).

For every four patients treated with topical capsaicin, one would have had the pain of diabetic neuropathy relieved who would not have had they been treated with placebo.

For comparison, oral anticonvulsant therapy for diabetic neuropathy in 66 treated patients in two trials yielded an NNT of 2.5 (1.8 - 4.0) [2].

Osteoarthritis

Three trials reported the use of capsaicin cream (0.025% in two, and 0.075% in one) four times daily for four weeks in osteoarthritis. The end point was articular tenderness or physicians global assessment of pain relief.

87/192 (45%) patients responded with capsaicin compared with 30/190 (16%) with placebo. The odds ratio favouring capsaicin was 4.4 (2.8 - 6.9) and NNT was 3.4 (2.6 - 4.8).

For every three patients treated with topical capsaicin, one would have had pain of osteoarthritis relieved who would not have been relieved had they been treated with placebo.

Postherpetic neuralgia

Only a single trial that fulfilled the inclusion criteria was available. Use of a 0.075% cream three or four times daily for six weeks resulted in pain relief in 4/16 patients with capsaicin compared with 1/16 patients with placebo.

Postmastectomy pain

A single trial of 0.075% cream four times daily for six weeks resulted in pain relief in 5/13 patients with capsaicin compared with 1/10 patients with placebo.

Psoriasis

Four trials reported on topical capsaicin 0.025% four times daily for 6 - 8 weeks in psoriasis. Psoriasis was rated by the degree of itching, scaling and erythema. The end point was a much better or better rating of overall appearance.

78/115 (68%) patients responded with capsaicin compared with 55/130 (42%) with placebo. The odds ratio favouring capsaicin was 2.8 (1.7 - 4.6) and NNT was 3.9 (2.7 - 7.4).

For every four patients treated with topical capsaicin, one would have had symptoms of psoriasis relieved who would not have been relieved had they been treated with placebo.

Cautious comments

The authors of the review suggested that blinding of trials of capsaicin might be difficult because of its irritant effects when applied to the skin. There may also be suggestions from some of the reports that skin irritation wears off with time, while analgesic effects may improve with time.

How much the placebo effect may influence the results is uncertain. These are difficult clinical conditions, and patients used the creams for up to eight weeks. Variability in the results in placebo groups can be seen from the figure to be from 0% to 50% of patients on placebo getting benefit. All the trials showed benefits over placebo.

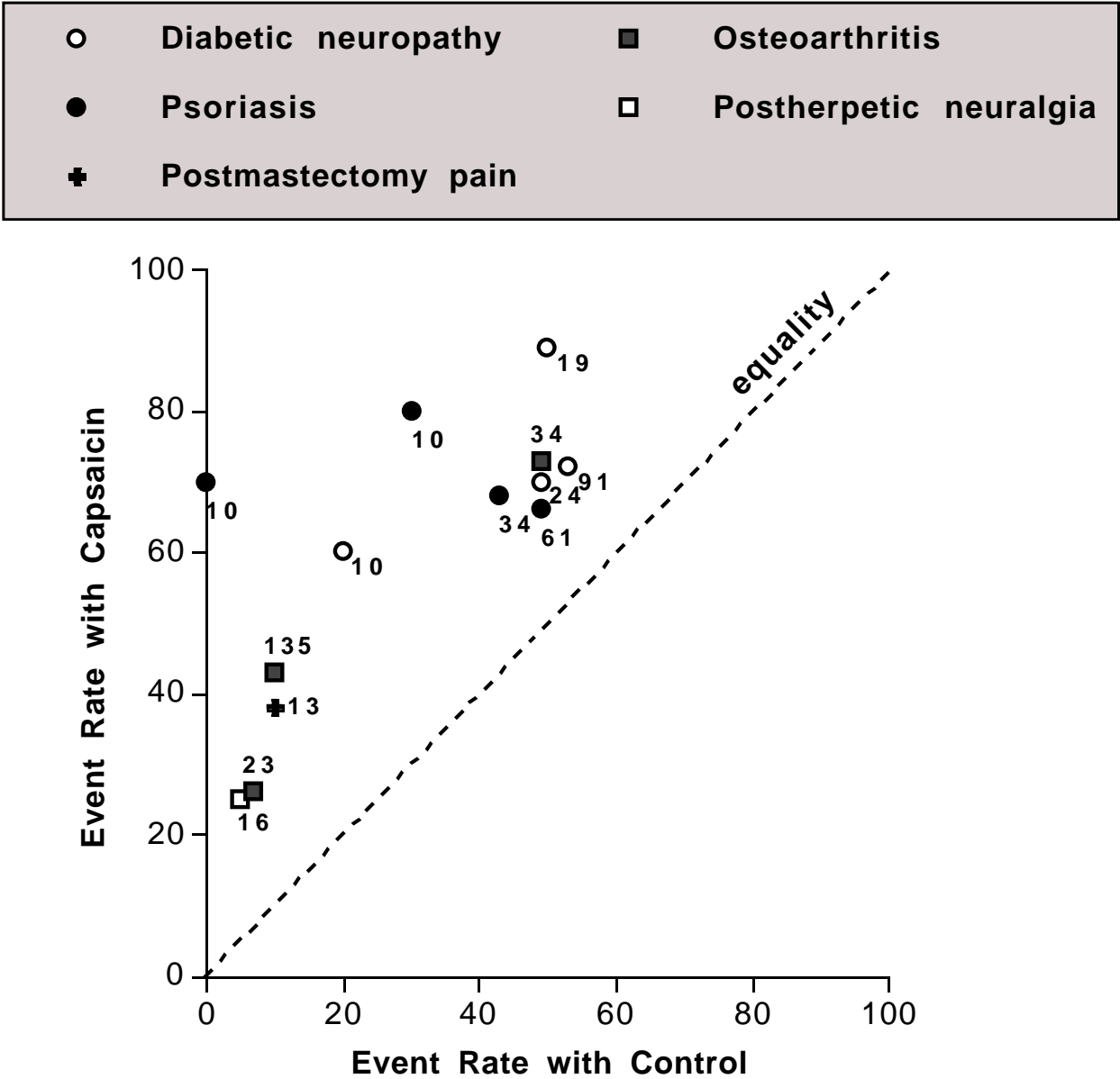
The numbers of patients treated in these studies was not large, but that is not unusual in these difficult clinical conditions [2]. The review did not include results of adverse effects, which is a shame, since any treatment choice should balance the probability of benefit and the risk of harm.

References:

1 WY Zhang, ALi Wan Po. The effectiveness of topically applied capsaicin. European Journal of Clinical Pharmacology 1994 46:517-22.

2 H McQuay, D Carroll, A Jadad, P Wiffen, A Moore. Anticonvulsant drugs for management of pain: a systematic review. British Medical Journal 1995 31 1: 1047-52.

L'Abbé plot for topical Capsaicin in



DRUG TREATMENT OF CHILDHOOD DEPRESSION

Background

Depression in children and adolescents is associated with social dysfunction, academic under achievement, and suicidal behaviour. It is generally under-recognised. Prevalence is estimated at 2% in primary school children, rising to 5% in adolescents.

Traditionally treatment has been psychological or psycho-analytical, family therapy being most popular in the UK. However, these are expensive treatments, some of unproven effectiveness.

Attention has therefore turned to antidepressant drugs, which are established in trials as effective in adult major depression. However, it is unsafe to extrapolate this evidence to young people, since these trials excluded children, in whom the condition certainly has a different epidemiology and may have a different aetiology.

Randomised controlled trials are needed to decide whether antidepressants work in childhood depression, since placebo responses are common and the condition frequently gets better naturally making other types of evidence impossible to interpret. A number of small RCTs of tricyclic antidepressants of variable methodological quality has been conducted, generally reporting non-significant trends in favour of treatment. Hazell et al [1] recently conducted a systematic review and meta-analysis of these trials.

Systematic review of RCTs

A comprehensive search strategy was used to identify trials from electronic databases, and from manual searches of English and non-English abstracts, bibliographies, and conference proceedings.

Twelve trials were identified, all but one reporting small, non-significant treatment benefits. Nine of the twelve studies identified could be used in the meta-analysis; exclusion criteria are described, but it is unclear why the authors excluded trials where data for children and adolescents could not be separated, since they do not present separate results for the two groups.

Results

There was one duplicate publication. Five trials presented their results as numbers improved (30/78 improved on treatment, 36/97 on placebo: pooled odds ratio 1.08 {95% CI 0.53 - 2.17}).

Six reported *effect sizes*, i.e. changes in the mean scores of the groups. Such *continuous outcomes* are more difficult to combine statistically than the above *dichotomous outcomes*, especially if standard deviations are not given - the authors had to assign this to some studies. Again, a trend towards improvement on tricyclics was seen, (pooled effect size = 0.35 {-

0.16 - 0.86}), a positive value representing improvement: since the 95% confidence interval includes 0 (no improvement), the result is not statistically significant.

The quality of the trials was investigated using published guidelines: the more rigorously conducted studies showed smaller treatment effects.

There are probably some unknown "negative" studies due to publication bias, which thus serves to strengthen the authors' conclusions.

Conclusions

- this high quality systematic review identified twelve trials of tricyclics, all but one weakly positive, and concludes that tricyclics are no more effective than placebo.
- the conclusions are supported by the likely effects of publication bias, and the less rigorous conduct of the more positive studies.
- over 50% responded to placebo
- a traditional narrative review might well have concluded tricyclics were effective, on a "small samples, no smoke without fire" principle.
- further drug research should concentrate on other agents, such as SSRIs
- this is a good starting point for any reader interested in meta-analysis.

Practice points

- there is no evidence that tricyclics are more effective than placebo for depression in children and adolescents
- any possible benefits are probably outweighed by the risks of toxicity
- these patients may well respond to non-drug strategies

Reference:

- 1 P Hazell, D O'Connell, D Heathcote, J Robertson, D Henry. Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis. British Medical Journal 1995 310: 897-901.

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